

contacting the oligonucleotides and nanoparticles in the salt solution for an additional period of time sufficient to allow sufficient additional oligonucleotides to bind to the nanoparticles to produce the stable nanoparticle-oligonucleotide conjugates.

434. The method of Claim 433 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

435. The method of Claim 434 wherein the nanoparticles are gold nanoparticles.

436. The method of Claim 435 wherein the moiety comprising a functional group which can bind to the nanoparticles is an alkanethiol.

A1 437. The method of Claim 433 wherein all of the salt is added to the water in a single addition.

438. The method of Claim 433 wherein the salt is added gradually over time.

439. The method of Claim 190 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

440. The method of Claim 439 wherein the salt is sodium chloride in a phosphate buffer.

441. The method of Claim 439 wherein nanoparticle-oligonucleotide conjugates are produced which have the oligonucleotides present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm<sup>2</sup>.

442. The method of Claim 441 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm<sup>2</sup>.

443. The method of Claim 442 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm<sup>2</sup> to about 40 picomoles/cm<sup>2</sup>.

444. A method of binding oligonucleotides to nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides, the oligonucleotides comprising at least one type of recognition-oligonucleotides, each of the recognition oligonucleotides comprising a spacer portion and a recognition portion, the spacer portion being designed so that it can bind to the nanoparticles; and

A<sup>1</sup> contacting the oligonucleotides and the nanoparticles under conditions effective to allow at least some of the recognition oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

445. The method of Claim 444 wherein each of the spacer portions of the recognition oligonucleotides has a moiety covalently bound thereto, the moiety comprising a functional group which can bind to the nanoparticles.

446. The method of Claim 444 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

447. The method of Claim 446 wherein the nanoparticles are gold nanoparticles.

448. The method of Claim 447 wherein the spacer portion comprises at least about 10 nucleotides.

449. The method of Claim 448 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

450. The method of Claim 449 wherein the bases of the nucleotides of the spacer are all adenines, all thymines, all cytosines, all uracils, or all guanines.

451. A method of binding oligonucleotides to nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides, the oligonucleotides comprising:

a type of recognition oligonucleotides; and

a type of diluent oligonucleotides;

contacting the oligonucleotides with the nanoparticles under conditions effective to allow at least some of each of the types of oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

A1 452. The method of Claim 451 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

453. The method of Claim 452 wherein the nanoparticles are gold nanoparticles.

454. The method of Claim 451 wherein each of the recognition oligonucleotides comprises a spacer portion and a recognition portion, the spacer portion being designed so that it can bind to the nanoparticles.

455. The method of Claim 454 wherein each of the spacer portions of the recognition oligonucleotides has a moiety covalently bound thereto, the moiety comprising a functional group which can bind to the nanoparticles.

456. The method of Claim 454 wherein the spacer portions of the recognition oligonucleotides comprises at least about 10 nucleotides.

457. The method of Claim 456 wherein the spacer portions of the recognition oligonucleotides comprises from about 10 nucleotides to about 30 nucleotides.

458. The method of Claim 454 wherein the bases of the nucleotides of the spacer are all adenines, all thymines, all cytosines, all uracils or all guanines.

459. The method of Claim 454 wherein the diluent oligonucleotides contain about the same number of nucleotides as are contained in the spacer portions of the recognition oligonucleotides.

460. The method of Claim 459 wherein the sequence of the diluent oligonucleotides is the same as the sequence of the spacer portions of the recognition oligonucleotides.

AI 461. The method of Claim 451 wherein the oligonucleotides comprise at least two types of recognition oligonucleotides.

462. A method of binding oligonucleotides to nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides having covalently bound thereto a moiety comprising a functional group which can bind to the nanoparticles, the oligonucleotides comprising:

a type of recognition oligonucleotides; and

a type of diluent oligonucleotides;

contacting the oligonucleotides with the nanoparticles in aqueous solution for a period of time sufficient to allow at least some of each of the types of oligonucleotides to bind to the nanoparticles;

adding at least one salt to the aqueous solution to form a salt solution; and

contacting the oligonucleotides and nanoparticles in the salt solution for an additional period of time sufficient to allow additional oligonucleotides of each of the types of oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

463. The method of Claim 462 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

464. The method of Claim 463 wherein the nanoparticles are gold nanoparticles.

465. The method of Claim 464 wherein the moiety comprising a functional group which can bind to the nanoparticles is an alkanethiol.

466. The method of Claim 462 wherein all of the salt is added to the water in a single addition.

~~467. The method of Claim 462 wherein the salt is added gradually over time.~~

A' 468. The method of Claim 462 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

469. The method of Claim 468 wherein the salt is sodium chloride in a phosphate buffer.

470. The method of Claim 462 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm<sup>2</sup>.

471. The method of Claim 470 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm<sup>2</sup>.

472. The method of Claim 471 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm<sup>2</sup> to about 40 picomoles/cm<sup>2</sup>.

473. The method of Claim 462 wherein each of the recognition oligonucleotides comprises a spacer portion and a recognition portion, the spacer portion having attached to it the moiety comprising a functional group which can bind to the nanoparticles.

474. The method of Claim 473 wherein the spacer portion comprises at least about 10 nucleotides.

475. The method of Claim 474 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

476. The method of Claim 473 wherein the bases of the nucleotides of the spacers are all adenines, all thymines, all cytosines, all uracils, or all guanines.

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477. The method of Claim 473 wherein the diluent oligonucleotides contain about the same number of nucleotides as are contained in the spacer portions of the recognition oligonucleotides.

478. The method of Claim 477 wherein the sequence of the diluent oligonucleotides is the same as the sequence of the spacer portions of the recognition oligonucleotides.

modified  
479. The method of Claim 462 wherein the oligonucleotides comprise at least two types of recognition oligonucleotides.

480. The method according to any one of claims 433 or 462 wherein the salt solution has an ionic strength sufficient to overcome at least partially the electrostatic attraction or repulsion of the oligonucleotides for the nanoparticles and the electrostatic repulsion of the oligonucleotides for each other. --

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